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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/408,761	09/29/99	DALE R	OLIG-020

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DIANNA L DEVORE
BOZICEVIC FIELD AND FRANCIS LLP
285 HAMILTON AVENUE SUITE 200
PALO ALTO CA 94301

EXAMINER	
LUNDGREN, J	
ART UNIT	PAPER NUMBER
1631	4

DATE MAILED: 12/23/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/408,761	DALE, RODERIC M. K.	
	Examiner	Art Unit	
	Jeffrey S. Lundgren	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *05 November 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-15, are drawn to an array comprising a plurality of modified oligonucleotides, classified in class 536, subclass 24.3.

II. Claims 16-17, are drawn to a method of analyzing, classified in class 435, subclass 6.

III. Claim 18, is drawn to a method of detecting a nucleic acid sequence in two or more collections of nucleic acid molecules, classified in class 435, subclass 6.

IV. Claim 19, is drawn to a method of using a label to detect hybridization with modified polynucleotide probes of known sequence, classified in class 435, subclass 6.

V. Claim 20, is drawn to a method of detecting nucleotide differences between the sequence of a target nucleic acid and the sequence of a reference nucleic acid, classified in class 435, subclass 6.

VI. Claim 21, drawn to a method for synthesizing modified oligonucleotides on a solid phase, classified in class 536, subclass 23.3.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, and II, III, IV and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1)

the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case a completely different method of detection can be utilized with the product of invention I.

Inventions I and IV are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case a completely different process of making an array can be utilized to make the array of invention I.

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods/processes, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups II, III, IV, V and VI are directed to methods that are functionally different, and are not required one for the other. Therefore, a search and examination of all the methods in one patent application would result in an undue burden, since the searches for the methods are not co-extensive, and the subject matter is divergent.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Ms. DeVore on December 3, 1999 a provisional election was made without traverse to prosecute the invention of group I, claims 1-15. Affirmation of this election must be made by applicant in replying to this Office action. Claims 16-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. For example, see page 38 of the current specification.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification invites the skilled artisan to experiment. The factors which must be considered in determining undue experimentation are set forth in *Ex parte Forman* 230 USPQ 546. The factors include: 1) quantity of experimentation; 2) the amount of guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the predictability of the prior art; 7) the breadth of the claims; and 8) the relative skill in the art.

It is the Examiner's position that undue experimentation is required for one of skill in the art to carry out the invention as claimed. The specification is significantly lacking in guidance, therefore, one of skill in the art would (more than likely) be unsuccessful in an effort to practice the invention. Ideally, the use of examples in a given specification typically serve to demonstrate at least the critical limitations and/or requirements in order to make/use an invention. However, this application lacks working examples that enable one of skill in the art to practice the methods as claimed. The nature of the invention requires the practitioner to understand the art with a relatively high level of skill. Additionally, the state of the prior art does not provide enablement where this

specification is lacking an enabling description, thus precluding one of skill in the art from practicing the invention as claimed. The prior art is not predictable with regards to the claimed invention, as the invention is claimed too broadly. The Examiner cites Dwyer et al. (U.S. Patent No. 5,986,083, November 16, 1999), in view of the current application as a means to illustrate how the specification does not enable the invention as claimed.

Dwyer et al., disclose modified oligonucleotides, wherein the modifications of the oligonucleotides comprise modifications in the backbone, at the 2'-ribose position, and end-capped backbone modifications (column 5, starting at line 16; and claim 19). The disclosure of Dwyer et al., experimentally demonstrates: 1) oligonucleotide composition stability under various conditions (i.e., endonucleases); *and* 2) the binding affinities between modified oligonucleotides and the complementary nucleic acids, as a function of the oligonucleotide modification.

Claims 1, and 15 are drawn to an array comprising a plurality of oligonucleotide compositions stably associated with the surface of a support, wherein the oligonucleotides of the composition are characterized by a binding affinity greater than that of a corresponding, non-modified oligonucleotide. However, this limitation requires undue experimentation by one of skill in the art since methods that allow one to predict binding affinities between an immobilized, modified capture nucleic acid and target nucleic acid are not currently known. Dwyer et al., state (column 3, starting with line 63):

> "Against DNA targets, both destabilization and stabilization were observed with the 2'-O-methyl modification to the sugar portion of the nucleosides, depending on the base sequence because some DNA sequences favor the A-form more than others whereas, stabilization was always observed against RNA targets. Moreover, we have observed dramatic differences in Tm with racemic methylphosphon[a]te oligomers hybridized to DNA and RNA targets."

This demonstrates a significant degree of unpredictability in the art with respect to the binding of modified oligonucleotides to target oligonucleotides. Additionally, experimental data not only supports this finding, but clearly demonstrates that modifications to oligonucleotides dictating binding affinities are complex and detailed, as demonstrated seen in Table II. A strategy of alternating phosphonate linkages proved to provide greater binding affinities (K_a) compared to oligonucleotides with complete phosphonate modifications in the backbone. Furthermore, the phosphodiester backbone without 2'-O-modifications had the highest K_a. Applicant fails to provide working examples that measure at least one binding affinity in relation to a modified oligonucleotide hybridized to a given target as claimed. In light of these findings, the Examiner concludes that the specification lacks significant guidance with respect to the array of modified oligonucleotide compositions with a binding affinity that is greater than that of an unmodified oligonucleotide, and is not enable for practice by one of skill in the art.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-9, and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims 2-9), and claim 15 are drawn to an array comprising a plurality of modified oligonucleotide compositions associated with the surface of a support, wherein the oligonucleotide compositions binding affinities are greater than that of a corresponding, non-modified oligonucleotide. However, it is not clear what the oligonucleotide compositions are binding to. Can the modified oligonucleotide compositions bind both RNA and DNA in with greater affinities? Also, what are the metes and bounds of the modifications to the oligonucleotides? Are all nucleotides modified at both the 2'-position? Are all nucleotides modified throughout the backbone?

Claim 14 is drawn to an array comprising a plurality of modified oligonucleotide compositions associated with the surface of a support, wherein a blocking moiety chemical is at one end or near the end of the oligonucleotide. How close does the blocking moiety have to be to the end in order to be an effective blocker of a nuclease?

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-9, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwyer et al. (U.S. Patent No. 5,986,083, November 16, 1999) in view of Miller et al. (WO 94/15619, 21 July, 1994).

Dwyer et al., disclose modified oligomers which exhibit nuclease stability, and also an enhanced binding affinity with the complementary target nucleic acid (see column 2, lines 24-28; and column 4 , lines 50-61). The modifications of the nucleic acid sequences include substituting phosphodiester linkages with phosphonates of various forms (see column 6, staring with line 55). Modifications of the oligonucleotide at the terminal end of the phosphodiester/phosphonate backbone are disclosed, and modifications at the 2'-ribose are disclosed (column 5, starting at line 16; and claim 19). Dwyer et al., demonstrate the complex relationship between binding affinity of the modified oligonucleotide sequences and the complementary targets (Example A), *and* the stability of the modified oligonucleotide sequences under conditions that normally degrade oligonucleotides (Examples B to H). Example H utilizes an immobilized target RNA (170 nt long), which hybridized to complementary nucleic acid sequences, wherein the complementary nucleic acids have varying degrees of chemical modifications. The affinity relationship of various modified sequences to the complementary target RNA is

demonstrated by the thermal dissociation temperature study (i.e., equivalent to T_m, as cited by applicant on page 10 of the current specification).

Dwyer et al., do not disclose an array of immobilized, modified oligonucleotides.

Chee et al., disclose an array of "high-density" (column 15, last paragraph) oligonucleotides immobilized on a solid support for hybridization assays.

From the combined references involving applications with oligonucleotide sequences, one of skill in the art would have had a reasonable expectation of success in producing the invention as claimed. One would have been motivated to integrate the 2'-O-alkyl, phosphonate, *and* end-blocking strategies with nucleic acids as taught by Dwyer et al., as a means of producing nuclease-stable oligonucleotide probes, wherein the probe binding affinities are controllable, with hybridization arrays as taught by Chee et al. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 10-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwyer et al. (U.S. Patent No. 5,986,083, November 16, 1999) in view of Miller et al. (WO 94/15619, 21 July, 1994) in view of Chee et al. (U.S. Patent No. 5,861,242, January 19, 1999).

Dwyer et al., disclose modified oligomers which exhibit nuclease stability, and also an enhanced binding affinity with the complementary target nucleic acid (see column 2, lines 24-28; and column 4 , lines 50-61). The modifications of the nucleic

acid sequences include substituting phosphodiester linkages with phosphonates of various forms (see column 6, staring with line 55). Modifications of the oligonucleotide at the terminal end of the phosphodiester/phosphonate backbone are disclosed, and modifications at the 2'-ribose are disclosed (column 5, starting at line 16; and claim 19). Dwyer et al., demonstrate the complex relationship between binding affinity of the modified oligonucleotide sequences and the complementary targets (Example A), *and* the stability of the modified oligonucleotide sequences under conditions that normally degrade oligonucleotides (Examples B to H). Example H utilizes an immobilized target RNA (170 nt long), which hybridizes to complementary nucleic acid sequences, wherein the complementary nucleic acids have varying degrees of chemical modifications. The affinity relationship of various modified sequences to the complementary RNA is demonstrated by the thermal dissociation temperature study (i.e., equivalent to Tm, as cited by applicant on page 10 of the specification).

Dwyer et al., do not disclose an array of immobilized, modified oligonucleotides. Dwyer et al., do not disclose the advantage of increased acid stability through various modifications of oligonucleotides.

Miller et al., disclose a modified oligonucleotide composition, wherein the 2'-OH of the ribose is modified with 2'-O-alkyl for improved acid stability (see Abstract; and contents therein of the disclosure).

Chee et al., disclose an array of "high-density" (column 15, last paragraph) oligonucleotides immobilized on a solid support for hybridization assays.

From the combine references involving applications with oligonucleotide sequences, one of skill in the art would have had a reasonable expectation of success in producing the invention as claimed. One would have been motivated to integrate the 2'-O-alkyl, phosphonate, *and* end-blocking strategies with nucleic acids as taught by Dwyer et al., as a means of producing nuclease-stable oligonucleotide probes, wherein the probe binding affinities are controllable, with hybridization arrays as taught by Chee et al. Furthermore, one of ordinary skill in the art would have recognized the increased stability of the oligonucleotide array under acidic conditions as taught by Miller et al. (an inherent property of the 2'-O-modification). Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

13. Also relevant to the claimed invention is the disclosure of Cummins et al. (Nucleic Acids Research *23*, pp. 2019-2024, **1995**). Cummins et al., disclose modified oligonucleotides and the thermodynamic stability (i.e., T_m; scales with binding affinities) between said modified oligonucleotide and the complementary target oligonucleotide (see pp. 2020-2021). Cummins et al., also disclose the utility of such modified oligonucleotides for therapeutics and diagnostics (p. 2024, first column, last paragraph).

14. No claims are allowable.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeffrey S. Lundgren whose telephone number is (703) 306-3221. The Examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM (EST), and alternating Fridays from 8:00 AM to 4:30 PM (EST).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1653 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Jeffrey S. Lundgren, Ph.D.

EGGERTON A. CAMPBELL
PRIMARY EXAMINER

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600